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Proposed Recommendations for Pertussis Treatment and Prophylaxis†

1. General Recommendation

The preferred antimicrobial agents for treatment and prophylaxis of pertussis are the macrolides. Erythromycin, clarithromycin, or azithromycin are appropriate first line agents for treatment or prophylaxis of pertussis for persons 6 months of age and older. (Please see Section 4 for treatment of infants <6 months of age). Trimethoprim-sulfamethoxazole can be used as an alternate antimicrobial agent. Providers should consider safety, evaluation of concurrent medications for potential interactions, adherence to the prescribed regimen, and cost when choosing a macrolide or alternative agent for any patient.

2. Treatment Recommendations

A. Erythromycin

- Erythromycin is available as an oral preparation as a base (enteric or film coated), as an ethylsuccinate salt, or as estolate or stearate esters. Some experts prefer the use of the estolate preparation in children because it achieves higher serum levels compared with the ethylsuccinate or stearate; however the estolate ester may not be available in the USA. The estolate ester is associated with an increased risk of drug-induced hepatitis in adults and should be avoided in pregnant women. The recommended dose of erythromycin for infants or children is 40 -50 mg/kg/day in four divided doses (maximum 2 gm/day); for adults the dose is 1-2 gm per day in 4 divided doses. The recommended duration of therapy to prevent bacteriologic relapse is 14 days.
- Erythromycin is classified as an FDA Pregnancy Category B* drug.
- An association between orally administered erythromycin and infantile hypertrophic pyloric stenosis (IHPS) in neonates has been reported
- Erythromycin is contraindicated in patients with known hypersensitivity to macrolides. Erythromycin should be used with caution when co-administered with other agents that are metabolized by the hepatic

cytochrome P-450 system including some agents used to treat convulsive disorders, antiretroviral drugs, and in patients taking astemizole or cisapride; synergystic drug interactions or elevated serum levels of these drugs leading to serious cardiac arrhythmias can result with concomittant erythromycin use (2). Drug interactions must be also considered when erythromycin is used concomittantly with theophylline, digoxin, oral anticoagulants, ergotamine or dihydroergotamine, lovastatin and other cholesterol-lowering drugs, and benzodiazipines; elevated and toxic levels of these drugs may result from drug interactions with erythromycin.

B. Newer macrolides (azithromycin, clarithromycin)

- Clinical studies have demonstrated that azithromycin and clarithromycin have microbiologic effectiveness comparable with erythromycin for treatment of pertussis in previously immunized individuals who are ≥6 months of age (3–8). In addition, adverse events were fewer and milder in the reported studies. No data are available on the effectiveness of azithromycin or clarithromycin for pertussis treatment in infants <1 month of age. As compared with erythromycin, these drugs have higher tissue concentration and longer half-lifes and have the advantage of being administered in fewer daily doses (1 or 2 doses per day), and in treatment courses that are shorter (5 –7 days). These agents are contraindicated in patients with known hypersensitivity to any of the macrolide class of antibiotics.

Azithromycin

- The recommended dose of azithromycin for treatment of pertussis in infants and older children is five days course taken as 10 mg/kg/day in a single dose on day 1 (maximum dose 500 mg) to be followed by 5 mg/kg/day (maximum dose 250 mg) taken in a single dose on days 2–5; for adults, the recommended dose is 500 mg/day taken in a single dose on day 1 followed by 250 mg/day in a single dose on days 2–5.
- Azithromycin is classified as FDA Pregnancy Category B* drug.

Clarithromycin

- The recommended dose of clarithromycin for treatment of pertussis in children is 15 mg/kg/day in two divided daily doses (maximum 500 mg per dose) for 7 days; for adults the recommended dose is 500 mg twice daily for 7 days.
- Clarithromycin is classified as a FDA Pregnancy Category C* drug.
- Clarithromycin is contraindicated in patients with known hypersensitivity to macrolides. Clarithromycin should be used with caution when co-administered with other agents that are metabolized by the hepatic cytochrome P-450 system including some agents used to treat convulsive disorders, antiretroviral drugs, and in patients taking astemizole or cisapride; synergystic drug interactions or elevated serum levels of these drugs leading to serious cardiac arrhythmias can result with concomittant clarithromycin use. Drug interactions must be considered when clarithromycin is used concomittantly with theophylline, digoxin, oral anticoagulants, ergotamine or dihydroergotamine, lovastatin and other cholesterol-lowering drugs, and benzodiazipines; elevated and toxic levels of these drugs can result from drug interactions when taken with clarithromycin.

C. Alternative agent –trimethoprim-sulfamethoxazole (TMP-SMZ)

- TMP-SMZ (or co-trimoxazole) may be used as an alternative agent in patients who are allergic to macrolides, who cannot tolerate macrolides, or who are infected, rarely, with a macrolide-resistant strain of *Bordetella pertussis*.
- The recommended dose in children is trimethoprim 8 mg/kg/day, sulfamethoxazole 40 mg/kg/day in two divided doses for 14 days. For adults, the recommended dose is trimethoprim 320 mg/day, sulfamethoxazole 1600 mg/day in two divided doses for 14 days.
- TMP-SMZ is classified as a FDA Pregnancy Category C* drug. Because of the risk of kernicterus, TMP-SMZ should not be given to pregnant

women, nursing mothers, premature neonates, or infants <2 months of age. The drug should be use with caution in elderly with underlying renal or hepatic impairment.

- TMP-SMZ is contraindicated in persons with known hypersensitivity to sulfanomide drugs and trimethoprim, liver damage, renal impairment, blood dyscrasias, or persons with G6PD deficiency. Following use of TMX-SMZ, common adverse events include allergic skin reactions, nausea, vomiting, and anorexia. Rarely, severe and fatal adverse events have been reported with sulfanamide use. These adverse events include Stevens-Johnson syndrome (severe eruptions around the mouth, anus, or eyes), toxic epidermal necrolysis, acute fulminant hepatic necrosis, agranulocytosis, and bone marrow suppression and other blood dyscrasias. Drug interactions must be considered when TMP-SMZ is used concomittantly with oral anticoagulant such as warfarin, drugs used to treat diabetes mellitus, such as glipizide, glyburide, chlorpropamide, tolbutamide and tolazamide, anticonvulsants such as dilantin, thiazide diuretics, and antiretroviral drugs; elevated and toxic levels of these drugs can result from drug interactions when taken with TMP-SMZ.

3. Chemoprophylaxis

- Erythromycin, azithromycin, and clarithromycin are appropriate first line agents for chemoprophylaxis of pertussis. TMP-SMZ is an alternative for persons who can not tolerate macrolides.
- The dosage, frequency, and duration of these drugs when used for prophylaxis are the same as for treatment.

4. Infants <6 months of age

A. Treatment.

- Data on the safety and efficacy of azithromycin and clarithromycin for persons <6 months of age are scant. The US Food and Drug

Administration has not licensed these drugs for use in infants <6 months of age.

- Only limited data from small clinical trials are available that confirm the microbiologic effectiveness of these agents in infants <6 months of age with pertussis, who are more likely to be partially or unimmunized and whose colonization is more likely to be prolonged compared with older, previously immunized individuals with pertussis. Nevertheless, considering theoretical rationale, in vitro effectiveness, safety and clinical data in older individuals with pertussis, and treatment adherence issues, any of the above macrolides may be used as a first line agent in infants 1-6 months of age. There are only limited data from presented or published case series on the use of azithromycin in infants<1 month of age (9). These studies report a decrease in adverse events with no increased risk or signal of IHPS in infants <1months of age who received azithromycin. For infants <1 month of age, the risk of developing severe pertussis and life threatening complications outweighs the potential risk of IHPS that is associated with macrolide use.
- The recommended pertussis treatment schedules for macrolides in infants 1 –5 month of age are as follows: erythromycin (whenever available the estolate preparation is preferred) given as 40-50 mg/kg/day in four divided doses (maximum 2 gm/day) for 14 days, or clarithromycin given as 15 mg/kg/day in two divided daily doses (maximum 500 mg per dose) for 7 days, or azithromycin given as 10 mg/kg/day in a single daily dose for five days.
- For treatment of pertussis in infants <1 month of age, azithromycin is the preferred drug of choice. Erythromycin is an acceptable alternative and can be given in a 14-day course as 40-50 mg/kg/day in 4 divided daily doses; whenever available, the estolate preparation is preferred. No published data are available on the use of clarithromycin in this age group. All infants <1 month of age who receive any macrolide should be

monitored for the development of IHPS, and, as with other antibiotics with limited experience, for other serious adverse events.

B. Chemoprophylaxis.

- For chemoprophylaxis, the benefits of administering a macrolide should be weighed according to the risk of disease and complications versus the potential adverse effects of the drug. Because of severe and sometimes fatal pertussis-related complications in infants under 6 months of age, postexposure chemoprophylaxis should be given.
- For infants <6 months of age, the recommended antibiotics for chemoprophylaxis are the same as those for treatment of pertussis. Infants <1 month of age who receive any macrolide should be monitored for the development of IHPS, and, as with other antibiotics with limited experience, for other serious adverse events.

References

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*APPENDIX: FDA PREGNANCY CATEGORIES

Category	Explanation
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy and there is no evidence of risk in later trimesters
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Table 1. Summary of oral macrolide treatment and chemoprophylaxis for pertussis by agegroup†

Agegroup	Erythromycin (14-day course)	Clarithromycin (7-day course)	Azithromycin (5-day course)
≥6 months	40-50 mg/kg/day in 4 divided doses (maximum 2 gm/day) X 14 days	15 mg/kg/day in 2 divided doses (maximum 500mg/dose) X 7 days	10 mg/kg/day in single dose on day 1 then 5mg/kg/day on Days 2 –5
1-5 months	As above (estolate preparation preferred if available)	As above	10mg/kg/day in single daily dose X 5 days
<1 month	As above (Use as alternate drug in doses above. Drug use is associated with elevated risk of IHPS)	Not recommended (Safety data unavailable)	Preferred drug. 10mg/kg/day in a single daily dose X 5 days. Only limited safety available.

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The recommended dose in children is trimethoprim 8 mg/kg/day, sulfamethoxazole 40 mg/kg/day in two divided doses for 14 days. For adults, the recommended dose is trimethoprim 320 mg/day, sulfamethoxazole 1600 mg/day in two divided doses for 14 days. Because of the risk of kernicterus, TMP-SMZ should not be given to pregnant women, nursing mothers, premature neonates, or infants <2 months of age.